

Remarks

Claims 1-201 are pending in the application. In response to a Restriction Requirement Applicant elected claims 1-88, 90-104, 112-117, 131, 165-193 for further prosecution. In response to the further Restriction Requirement with respect to claims 39-68, 94-97, 179-180, and 182-184, and with respect to linking claims 1, 86 and 145, Applicant elected SEQ ID NO: 43 as to claims 39-48; SEQ ID NOs: 93 and 94, and 188 and 189 as to claims 64 and 65; respectively; SEQ ID NOs: 93 and 188 as to claims 69, 97, and 182. Per Applicant's response to the Restriction Requirements, the Examiner has withdrawn claims 21, 29, 30, 49-63, 89, 105-111, 118-144, 146-164, and 194-200 from further consideration. Claims 1-20, 22-28, 31-48, 64-88, 90-104, 112-117, 145, 165-193 and 201 are under consideration.

Claims 1-20, 22-28, 31-38, 70-88, 90-93, 98-104, 112-117, 145, and 165-193 stand rejected. Claims 39-48, 64-69, 94-97, and 201 are objected to.

Claims 23-25, 36-38, 175, and 176 are canceled by the present Amendment. Claims 1, 2, 5-19, 22, 27, 28, 31-35, 39-48, 64-68, 69-87, 91-97, 116, 145, 165, 167, 169, 170, 172-174, 177-184 are currently amended. Support for the amendments can be found in claims as filed, and throughout the specification, *e.g.*, in paragraphs 105-182 and in the exemplification (see, *e.g.*, paragraphs 263-452).

No new matter has been added by the present Amendment. Applicant specifically reserves the right to pursue the subject matter of the canceled or amended claims in a related application. The present Amendment is introduced for the sole purpose of furthering prosecution. Applicant respectfully requests reexamination and reconsideration of the case in light of the present Amendment and the following Remarks. Each of the rejections levied in the Office Action is addressed individually below.

Sequence Listing

Applicant submits herewith a substitute Sequence Listing and has amended the specification (1) to incorporate the substitute Sequence Listing, and (2) to ensure that all sequences listed in the specification are properly associated with the requisite sequence identifiers as set forth in the substitute Sequence Listing (37 C.F.R. § 1.821(d)).

Applicant notes that the requirements of 37 C.F.R. § 1.52(e)(3)(ii), (4), and (6) are not applicable to computer program listings, sequence listings, and tables submitted as text files via

EFS-Web. Pursuant to 37 C.F.R. § 1.821, a patent application which discloses nucleotide and/or amino acid sequences must contain both “a paper copy” of the sequence listing (37 C.F.R. § 1.821(c)) and a computer readable form (CRF) of the sequence listing (37 C.F.R. § 1.821(e)). According to the Legal Framework for EFS-Web (September, 2008), if a sequence listing text file submitted via EFS-Web complies with the requirements of 37 C.F.R. § 1.824(a)(2)-(6) and (b) (*i.e.*, is a compliant sequence listing ASCII text file), the text file will serve as both the paper copy required by 37 C.F.R. § 1.821(c) and the CRF required by 37 C.F.R. § 1.821(e). Thus a statement under 37 C.F.R. § 1.821(f) (indicating that the paper copy and CRF copy of the sequence listing are identical) is unnecessary.

Information Disclosure Statement (IDS)

The Examiner states that the IDS submitted on December 28, 2004 is non-compliant on the grounds that the last citation on page 6 (“International Search Report issued for corresponding PCT application PCT/US03/30508,” referred to herein as “the ‘508 ISR”)) does not contain a date. Applicant respectfully submits that a copy of the ‘508 ISR was submitted along with the IDS, and that the date (*i.e.*, September 16, 2004) was *clearly* printed on the front of the ‘508 ISR. Applicant further acknowledges that, on page 4 of the Office Action, the Examiner stated that the information contained in the ‘508 ISR “has been considered by the examiner on the merits.” Applicant thanks the Examiner for considering the ‘508 ISR, and in light of this fact, Applicant respectfully requests that the Examiner indicate this by placing his initials next to the ‘508 ISR citation as listed on page 6 of the IDS and mailing a copy to Applicant along with the next Office Communication. Applicant also requests that the ‘508 ISR be printed on any patent issued from this application.

Objection to the Claims

On page 2 of the Office Action (under “Disposition of the Claims,” line 7), the Examiner indicated that claims 39-48, 64-69, 94-97 and 201 were objected to. The Office Action, however, did not provide any reasons for the objection. Applicant respectfully requests that (1) the objection be withdrawn, or (2) the Examiner reissues the instant Office Action along with a basis for the Examiner’s objection to the claims and provides an opportunity for Applicant to respond to the objection.

Objection to the Specification

The Examiner has objected to the specification on the grounds that page 84 is blank. Applicant respectfully submits that page 84 was present at the time of the filing. Indeed, the application as published (U.S. Patent Publication Number 2004/0242518) contains the content of page 84 of the specification as filed. Applicant respectfully directs the Examiner to paragraphs 265-266 in the published application for the content of page 84 of the specification as filed. Applicant respectfully requests that the objection be removed.

Rejection under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite

Claims 145 and 165-193 stand rejected under 35 U.S.C. § 112, second paragraph, on the grounds that they are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner states that claim 145 depends from a claim that has been withdrawn from consideration. Applicant thanks the Examiner for pointing out this inadvertent error and has amended claim 145 to correct the dependency of that claim. Applicant, therefore, respectfully requests that the rejection be removed.

The Examiner states that claims 165-193 all recite or depend from claims that recite “an RNAi inducing entity.” The Examiner alleges that this term is not an art-recognized term and that the specification does not provide any specific definition of what is embraced by this term. While not agreeing with the Examiner, and *solely* in order to further prosecution, Applicant has amended claim 165 to recite an “siRNA or shRNA molecule” instead of an “RNAi inducing entity.” Applicant, therefore, respectfully requests that the rejection be removed.

Rejection under 35 U.S.C. § 103(a) as allegedly being obvious

Claims 1-20, 22-28, 31-38, 70-88, 90-93, 98-104, 112-117, 165-178 and 185-193 stand rejected under 35 U.S.C. § 103(a) on the grounds that they are unpatentable over Tuschl *et al.* (U.S. Patent Publication Number 2004/0259247) and Beach *et al.* (U.S. Patent Publication Number 2002/0162126) in view of Abe *et al.* (2001, *Eur. J. Pharm. Sci.*, 13:61-69), Gitlin *et al.* (2002, *Nature*, 418:430-34), Brummelkamp *et al.* (2002, *Science*, 296:550-53), and Paddison *et al.* (2002, *Genes Dev.*, 16:948-58). The Examiner alleges that Tuschl teaches the use of siRNA

and that siRNA may be used to inhibit viral genes; that Beach teaches siRNA and shRNA compounds; that Abe teaches inhibiting influenza virus using antisense oligonucleotides; that Gitlin teaches inhibiting polio virus genes via the use of siRNA, including targeting conserved regions; and that Brummelkamp and Paddison both teach use of vectors using pol III promoters for effective expression of siRNA and shRNA compounds *in vivo*.

The Examiner alleges that “there is a need in the art to inhibit influenza virus” and that the art has shown (1) inhibition of influenza virus targeting various genes via antisense compounds, (2) that siRNA is more effective and safer than antisense compounds, (3) a means of siRNA delivery was known, including vectors, (4) that multiple conserved regions of genes should be targeted, and (5) that siRNA can be optimized to inhibit gene expression many fold.

For all these reasons, the Examiner concluded that the claims were *prima facie* obvious. Applicant disagrees and responds to this rejection of the claims as follows.

Response with respect to claims 1-20, 22-28, 31-38, 70-85 and 112-117

Neither Tuschl nor Beach disclose or suggest a composition comprising an siRNA or shRNA molecule targeted to a transcript of a respiratory virus, which molecule comprises (a) a first single-stranded RNA molecule consisting of a sequence that is homologous to highly conserved region of the target transcript among a plurality of variants of the virus and comprises at least 15 consecutive nucleotides, (b) a second single-stranded molecule that comprises a region that is complementary to the first strand, and (c) an RNA duplex formed by the first and second RNA molecules hybridizing together, wherein the siRNA or shRNA molecule inhibits production of the virus by at least 2 fold, relative to the level that would be present in the absence of the siRNA or shRNA molecule, in cells infected by the virus. Secondary references Abe, Gitlin, Brummelkamp, and Paddison fail to cure the shortcomings of Tuschl and Beach.

The Examiner relies on Tuschl’s disclosure of siRNA molecules, and Tuschl’s suggestion that siRNA may be used to inhibit a virus. Applicant submits, however, that Tuschl provides only a very general description of siRNA technology and fails to describe an siRNA molecule as recited in claim 1. For example, Tuschl fails to describe an siRNA that inhibits production of a respiratory virus by at least 2 fold by targeting a conserved region among variants of such a virus.

The Examiner relies on Beach's disclosure for expression of siRNA from a vector. However, Beach fails to describe an siRNA that is recited by claim 1, and shares the shortcomings of Tuschl, outlined above, with respect to that claimed invention.

The Examiner relies on Abe's disclosure of antisense technology directed to influenza virus. Abe is deficient for the same reasons as Tuschl and Beach. Abe fails to describe targeting to conserved sequences among variants of a respiratory virus, or forming a RNA duplex that inhibits virus production by at least 2 fold. The Examiner similarly relies on Brummelkamp and Paddison for use of vectors, *e.g.*, for teaching use of vectors with pol III promoters. This is inapposite to the invention recited in claim 1 for the same reasons that Tuschl, Beach, and Abe, alone or in combination, fail to describe an siRNA that inhibits production of a respiratory virus by at least 2 fold by targeting a conserved region among variants of such a virus.

The Examiner relies on Gitlin for allegedly disclosing that using dsRNA directed to multiple conserved RNA target sequence will provide an improved strategy of inhibiting or providing cellular immunity to human viruses. Gitlin, however, fails to describe targeting to conserved sequences among variants of a respiratory virus, or forming a RNA duplex that inhibits virus production by at least 2 fold. Accordingly, Gitlin does not teach or suggest an siRNA that inhibits production of a respiratory virus by at least 2 fold by targeting a conserved region among variants of such a virus.

Accordingly, for the reasons above, Tuschl and Beach, alone or in combination with Abe, Gitlin, Brummelkamp, and Paddison, fail to disclose the invention recited in claim 1. Applicant, therefore, respectfully requests that the Examiner withdraws the obviousness rejection of claim 1 and dependent claims 2-20, 22-28, 31-38, 70-85 and 112-117.

Response with respect to claims 86-88, 90-93, and 98-104

Neither Tuschl nor Beach disclose or suggest a vector comprising a nucleic acid that encodes an siRNA or shRNA molecule, which molecule comprises (a) a first single-stranded RNA molecule consisting of a sequence that is homologous to highly conserved region of the target transcript among a plurality of variants of the virus and comprises at least 15 consecutive nucleotides, (b) a second single-stranded molecule that comprises a region that is complementary to the first strand, and (c) an RNA duplex formed by the first and second RNA molecules hybridizing together, wherein the siRNA or shRNA molecule inhibits production of

the virus by at least 2 fold, relative to the level that would be present in the absence of the siRNA or shRNA molecule, in cells infected by the virus. Secondary references Abe, Gitlin, Brummelkamp, and Paddison fail to cure the shortcomings of Tuschl and Beach.

The Examiner relies on Tuschl's disclosure of siRNA molecules, and Tuschl's suggestion that siRNA may be used to inhibit a virus. As stated above, Tuschl's disclosure cited by the Examiner failed to describe an siRNA molecule that inhibits production of a respiratory virus by at least 2 fold by targeting a conserved region among variants of such a virus, and, further, Tuschl failed to describe a vector encoding such an siRNA molecule.

The Examiner relies on Beach's disclosure for expression of siRNA from a vector. However, Beach fails to describe composition recited by claim 86, and shares the shortcomings of Tuschl, with respect to that claimed invention: an siRNA molecule that inhibits production of a respiratory virus by at least 2 fold by targeting a conserved region among variants of such a virus.

The Examiner relies on Abe's disclosure of antisense technology directed to influenza virus. Abe is deficient for the same reasons as Tuschl and Beach. Abe fails to describe targeting to conserved sequences among variants of a respiratory virus, or forming a RNA duplex that inhibits virus production by at least 2 fold. The Examiner similarly relies on Brummelkamp and Paddison for use of vectors, specifically for teaching use of vectors with pol III promoters. This is inapposite to the invention recited in claim 86 for the same reasons that Tuschl, Beach, and Abe, alone or in combination, fail to describe an siRNA that inhibits production of a respiratory virus by at least 2 fold by targeting a conserved region among variants of such a virus.

The Examiner relies on Gitlin for allegedly disclosing that using dsRNA directed to multiple conserved RNA target sequence will provide an improved strategy of inhibiting or providing cellular immunity to human viruses. Gitlin, however, fails to describe targeting to conserved sequences among variants of a respiratory virus, or forming a RNA duplex that inhibits virus production by at least 2 fold. Accordingly, Gitlin does not teach or suggest an siRNA that inhibits production of a respiratory virus by at least 2 fold by targeting a conserved region among variants of such a virus.

Accordingly, for the reasons above, Tuschl and Beach, alone or in combination with Abe, Gitlin, Brummelkamp, and Paddison, fail to disclose the invention recited in claim 86. Applicant

requests that the Examiner withdraws the obviousness rejection of claim 86 and dependent claims 87, 88, 90-93, and 98-104.

Response with respect to claim 145

Neither Tuschl nor Beach disclose or suggest a composition comprising an siRNA or shRNA molecule produced by a method comprising steps of:

- (a) identifying a sequence of a target transcript that is highly conserved among a plurality of variants of a respiratory virus and comprises at least 15 consecutive nucleotides;
- (b) synthesizing a first RNA strand comprising the sequence;
- (c) synthesizing a second RNA strand comprising a sequence that is complementary to the first strand;
- (d) forming a duplex by combining the first and second strands;
- (e) repeating steps (a) through (d) to produce a plurality of siRNA or shRNA molecules;
- (f) testing each siRNA or shRNA molecule from step (e) for its ability to inhibit production of the respiratory virus in an cell infected by the virus; and
- (g) identifying a siRNA or shRNA molecule that inhibits at least 2 fold of the virus production.

Secondary references Abe, Gitlin, Brummelkamp, and Paddison fail to cure the shortcomings of Tuschl and Beach.

The Examiner relies on Tuschl's disclosure of siRNA molecules, and Tuschl's suggestion that siRNA may be used to inhibit a virus. Applicant submits, however, that Tuschl provides only a very general description of siRNA technology and fails to describe an siRNA molecule as recited in claim 145. For example, Tuschl fails to describe an siRNA molecule that produced by a method of synthesizing a first RNA strand comprising a sequence that is highly conserved among a plurality of variants of a respiratory virus, and that is identified by its ability to that inhibits production of a respiratory virus by at least 2 fold.

The Examiner relies on Beach's disclosure for expression of siRNA from a vector. However, Beach fails to describe an siRNA that is recited by claim 145, and shares the shortcomings of Tuschl, outlined above, with respect to that claimed invention. Beach fails to describe an siRNA molecule that produced by a method of synthesizing a first RNA strand

comprising a sequence that is highly conserved among a plurality of variants of a respiratory virus, and that is identified by its ability to that inhibits production of a respiratory virus by at least 2 fold.

The Examiner relies on Abe's disclosure of antisense technology directed to influenza virus. Abe is deficient for the same reasons as Tuschl and Beach. Abe fails to describe an siRNA molecule that produced by a method of synthesizing a first RNA strand comprising a sequence that is highly conserved among a plurality of variants of a respiratory virus, and that is identified by its ability to that inhibits production of a respiratory virus by at least 2 fold. The Examiner similarly relies on Brummelkamp and Paddison for use of vectors, specifically for teaching use of vectors with pol III promoters. This is inapposite to the invention recited in claim 145 for the same reasons that Tuschl, Beach, and Abe, alone or in combination, fail to describe an siRNA molecule that produced by a method of synthesizing a first RNA strand comprising a sequence that is highly conserved among a plurality of variants of a respiratory virus, and that is identified by its ability to that inhibits production of a respiratory virus by at least 2 fold.

The Examiner relies on Gitlin for allegedly disclosing that using dsRNA directed to multiple conserved RNA target sequence will provide an improved strategy of inhibiting or providing cellular immunity to human viruses. Gitlin, however, fails to describe targeting to conserved sequences among variants of a respiratory virus, or forming a RNA duplex that inhibits virus production by at least 2 fold. Accordingly, Gitlin does not teach or suggest an siRNA that inhibits production of a respiratory virus by at least 2 fold by targeting a conserved region among variants of such a virus.

Accordingly, for the reasons above, Tuschl and Beach, alone or in combination with Abe, Gitlin, Brummelkamp, and Paddison, fail to disclose the invention recited in claim 145. Applicant requests that the Examiner withdraws the obviousness rejection of this claim.

Response with respect to claims 165-178 and 185-193

Neither Tuschl nor Beach disclose or suggest a composition comprising: an siRNA or shRNA molecule, wherein the molecule is targeted to an influenza virus transcript, which molecule comprises (a) a first single-stranded RNA molecule consisting of a sequence that is homologous to highly conserved region of the target transcript among a plurality of variants of

the virus and comprises at least 15 consecutive nucleotides, (b) a second singled-stranded molecule that comprises a region that is complementary to the first strand, and (c) an RNA duplex formed by the first and second RNA molecules hybridizing together, wherein the siRNA or shRNA molecule inhibits production of the virus by at least 2 fold, relative to the level that would be present in the absence of the siRNA or shRNA molecule, in cells infected by the virus; and a delivery agent selected from the group consisting of: cationic polymers, modified cationic polymers, peptide molecular transporters, surfactants suitable for introduction into the lung, neutral or cationic lipids, liposomes, non-cationic polymers, modified non-cationic polymers, bupivacaine, and chloroquine. Secondary references Abe, Gitlin, Brummelkamp, and Paddison fail to cure the shortcomings of Tuschl and Beach.

The Examiner relies on Tuschl's disclosure of siRNA molecules, and Tuschl's suggestion that siRNA may be used to inhibit a virus. Applicant submits, however, that Tuschl provides only a very general description of siRNA technology and fails to describe an siRNA molecule as recited in claim 165. For example, Tuschl fails to describe an siRNA that inhibits production of a respiratory virus by at least 2 fold by targeting a conserved region among variants of such a virus, or any of the delivery agents recited in claim 165.

The Examiner relied on Beach's disclosure for expression of siRNA from a vector. However, Beach failed to describe an siRNA that is recited by claim 165, and shares the shortcomings of Tuschl, outlined above, with respect to that claimed invention: Beach fails to describe an siRNA that inhibits production of a respiratory virus by at least 2 fold by targeting a conserved region among variants of such a virus, or any of the delivery agents recited in claim 165.

The Examiner relies on Abe's disclosure of antisense technology directed to influenza virus. Abe is deficient for the same reasons as Tuschl and Beach. Abe fails to describe targeting to conserved sequences among variants of a respiratory virus, or forming a RNA duplex that inhibits virus production by at least 2 fold. The Examiner similarly relies on Brummelkamp and Paddison for use of vectors, specifically for teaching use of vectors with pol III promoters. This is inapposite to the invention recited in claim 1 for the same reasons that Tuschl, Beach, and Abe, alone or together fail; none of these references to describe an siRNA that inhibits production of a respiratory virus by at least 2 fold by targeting a conserved region among variants of such a virus, or any of the delivery agents recited in claim 165.

The Examiner relies on Gitlin for allegedly disclosing that using dsRNA directed to multiple conserved RNA target sequence will provide an improved strategy of inhibiting or providing cellular immunity to human viruses. Gitlin, however, fails to describe targeting to conserved sequences among variants of a respiratory virus, or forming a RNA duplex that inhibits virus production by at least 2 fold. Accordingly, Gitlin does not teach or suggest an siRNA that inhibits production of a respiratory virus by at least 2 fold by targeting a conserved region among variants of such a virus.

Accordingly, for the reasons above, Tuschl and Beach, alone or in combination with Abe, Gitlin, Brummelkamp, and Paddison, fail to disclose the invention recited in claim 165. Applicant requests that the Examiner withdraws the obviousness rejection of claim 1 and its dependent claims, claims 166-178 and 185-193.

Conclusion

For all of the reasons set forth above, each of the rejections in this case should be removed and the application should proceed to allowance. A Notice to that effect is respectfully requested.

If, at any time, it appears that a phone discussion would be helpful, the undersigned would greatly appreciate the opportunity to discuss such issues at the Examiner's convenience. The undersigned can be contacted at (617) 248-4903.

Please charge any fees that may be required for the processing of this Response, or credit any overpayments, to our Deposit Account Number 03-1721, referencing Attorney's Docket Number 0492611-0506 (MIT 9926).

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